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PILLSBURY WINTHROP, LLP
P.O. BOX 10500
MCLEAN, VA 22102

EXAMINER

WOITACH, JOSEPH T

ART UNIT	PAPER NUMBER
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1632

21

DATE MAILED: 09/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application N .

09/435,629

Applicant(s)

STICE ET AL.

Examin r

Joseph T. Voitach

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-- The MAILING DATE f this communication appears n the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 June 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) 91-120 is/are pending in the application.
- 4a) Of the above claim(s) 106-120 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☐ Claim(s) 91-105 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ 6) ☐ Other:

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Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on June 12, 2003, paper number 20, has been entered.

DETAILED ACTION

This application filed November 8, 1999, is a divisional of 08/766,939, filed December 16, 1996, now US Patent 5,994,619, which is a continuation in part of 08/626,054, filed April 1, 1996, now US Patent 5,905,042.

As indicated in the Advisory Action mailed March 5, 2003, paper number 18, Applicants' after final amendment filed February 12, 2003, paper number 17, has been entered. Claims 91, 101 and 102 were amended. Claims 91-120 are pending.

Election/Restriction

As indicated in the previous office action, Applicant's election without traverse of group II, claims 79-90, in Paper No. 9, is acknowledged. It is noted that Applicant's election of group II

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was drawn to a stable culture/cell line of cultured inner cell mass cells capable of prolonged passage, classified in class 435, subclass 325 (see restriction requirement, paper number 7).

More specifically, independent claim 79 encompassed a stable culture of CICM derived from two bovine of different genetic complement wherein the cells are capable of generating a chimeric bovine.

Claims 106-120 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: claims 106-120 encompass stable cell lines from a completely different species than previously claimed or considered. The claims are drawn to different products which are materially different one from the other comprising different genetic material and cellular markers. Further, each of the products are capable of separate and different uses. Additionally, the ability and specific methods to isolate, propagate, manipulate and maintain totipotent cells in culture for one species would not make obvious the ability to practice those methods in another species.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 106-120 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

It is noted the restriction presented above was set forth in the final office action mailed August 12, 2002, paper number 14. Additionally, it is noted that Applicants indicate in opening remarks (page 2 of amendment) that claims 106-120 are canceled, however there is no indication

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of this in the amendments to the claims (page 1-2). Therefore, claims 91-120 are considered pending. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 106-120 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 91-105 are currently under examination.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Objections

Claim 91 objected to because the acronym for CICM was not set forth in the claims is withdrawn. The amendments to the claims to recite 'cultured inner cell mass' has obviated the basis of the objection.

Claims 101 and 102 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim is withdrawn. The

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amendments to the claims to make them independent claims has obviated the basis of the objection.

Double Patenting

Applicant is advised that should claim 91 be found allowable, claims 101 and 102 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

In the instant case, the teaching of the present specification provides that the structural and physical characteristics of bovine CICM cells (claim 101), and the teaching of the specific markers of alkaline protease positive and cytokeratin 18 negative (claim 102) are inherent properties used to identify CICM cells. Therefore, while claim 91 claims any bovine CICM cell and newly amended claims 101 and 102 set forth specific characteristics associated with CICM cells, because the physical characteristics and specific markers are inherently present on the CICM cells, this limitation would not further limit the CICM cells being claimed, and each of the claims encompass exactly the same subject matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 91-105 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 91-105 also stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

In the instant case, the composition of totipotent transgenic cells comprising two populations of cells one which expresses a transgene and one that does not express a transgene is considered new matter. Unlike the previous claims wherein the genetic complement of the two types of cells in the composition were clearly different, the present claims are drawn to identical cells which demonstrate differences in expression. Upon review of the specification there is no specific recitation of this limitation. The specification defines a transgene and transgenic as exogenous genetic material incorporated into the germ and somatic cells of an animal

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(specification, page 18). The selection conditions pointed to on page 41, lines 1-13 do not support a transgenic cell line that contains both cells that express and do not express the gene of interest. To the contrary the conditions are used to obtain a population of cells wherein all the cells express the gene of interest. The support pointed to in Example 5 describes the differentiation of CICM cells, and thus does not support totipotent cells which differentially express a gene of interest. Upon review of the specification, the only compositions which have the ability to differentially express a gene are compositions of cells which genetically different which were combined to provide a chimeric composition of cells. Unlike the composition encompassed by the present claims, these chimeric compositions comprise different populations of cells.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to

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determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure" (emphasis added). In the instant case a review of the claims and portions of the specification pointed to by Applicants does not support the limitations presently set forth in the claims. Further, a review of the entire specification the only compositions which meet the limitations set forth in the present claims are compositions of genetically different cells. The present specification fails to provide literal or figurative support for a transgenic totipotent bovine CICM cell line which contains two populations of cells, one which expresses and one that does not express the transgene in said cell line.

Applicants argue that the claimed invention is described numerous times in the specification. For support Applicants point to methods describing the transfection of CICM cells with a selectable marker *in vitro* and selecting cells transgenic cells (pages 3-4). Applicants argue that 'persons skilled in the art know that the cells that are exposed to heterologous DNA comprising a transgene may fail to express the transgene' (page 4), and that the specification 'expressly describes making the claimed invention (page 4). Applicants' arguments have been fully considered, but not found persuasive see (pages 3-5).

Initially, it is noted there is no literal support in the specification for the instant claims. Turning to the figurative support pointed to by Applicants, it is noted that neither at the specific citations nor anywhere else in the specification do any of the methods indicate making the instantly claimed composition. To the contrary the methods are directed to making CICM cells

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comprising heterologous DNA. For example, the method at pages 11-12 states (vi) inserting heterologous DNA into said CICM cells; (vii) selecting for transgenic CICM cells and similar method steps generally set forth at page 19. In neither case is there an indication that the instantly claimed composition is being generated, rather only CICM cells containing a transgene. The original elected claims were directed to a composition comprising CICM cells from two genetic complements to provide a chimeric embryo (claim 79). The method pointed to by Applicants in the specification provides introducing CICM cells, with or without a transgene, into an embryo to form a chimeric embryo. In each case, the specification provides no support for generating or using the instantly claimed composition. This instant situation is analogous to *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 45 USPQ2d 1498 (Fed. Cir. 1998) where under certain circumstances, omission of a limitation can raise an issue regarding whether the inventor had possession of a broader, more generic invention. (In *Gentry Gallery*, the “court’s determination that the patent disclosure did not support a broad meaning for the disputed claim terms was premised on clear statements in the written description that described the location of a claim element--the control means’ --as the only possible location’ and that variations were outside the stated purpose of the invention.’ *Gentry Gallery*, 134 F.3d at 1479, 45 USPQ2d at 1503. In the instant case, while *in vitro* transfection methods may result in some cells receiving and expression a heterologous polynucleotide and some cells not expressing the transgene, there is no clear indication that the instantly claimed invention was specifically contemplated anywhere in the instant specification. Possession may be shown by actual reduction to practice,

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clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics (as it relates to the claimed invention as a whole) such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Pfaff v. Wells Electronics, Inc.*, 48 USPQ2d 1641, 1646 (1998). In the instant case the specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d at 1116. Further, relying on inherent properties of an intermediate product which may result from practicing a method described in the specification fails to demonstrate that Applicants' contemplated or were in possession of the instantly claimed composition of cells.

Therefore, for the reasons above and of record, the rejection is maintained.

Claims 91, 96 and 97 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for expressing the differentiation-inhibiting gene LIF, does not reasonably provide enablement for any other of the genes specifically recited in the claims or the specification. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue

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experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The claims are drawn to a composition of CICM cells which express a differentiating-inhibiting gene. Claim 97 recites several specific genes and the present specification provides references for other genes known in the art. The basis of the of the instant rejection is not whether one could transduce a cell and express any of the specific genes taught, rather it focuses on the failure of the specification and art of record to teach any gene besides LIF which would be considered differentiating-inhibiting gene. The specification specifically defines a differentiation inhibiting gene as "any nucleic acid sequence which inhibits the differentiation of ICMs" (top of page 17). At the time of filing the importance of LIF in the culture media was well known and demonstrated to prevent differentiation of embryonic germ cells, ICM cells and

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embryonic stem cells. However, upon review of the references cited in the present specification (page 17) and a review of the art regarding the specific genes recited in the claims, the genes described would not serve as differentiation-inhibiting genes. Other than LIF, each of the genes specifically taught would be considered markers of differentiation. Further, it is noted that the claims are drawn specifically to totipotent cells, however each of the marker genes are expressed in cells which are not totipotent. For example Oct-3 is described by Okamoto *et al.* (Cell, 1990) as expressed in carcinoma cells, however these cells would not be considered to be totipotent or capable of giving rise to an animal. Rosner *et al.* (Nature, 1990) clearly teach that Oct-3 is expressed in totipotent and pluripotent cells. In each case the expression of Oct-3. The LIF receptor is present in many cell types and its presence alone, i.e. in the absence of LIF, would not prevent a cell from differentiating. T antigen and other oncogenes are known, however at the time of filing these were used to transform and/or immortalize a cell, not prevent its differentiation. At the time of filing numerous cell lines known and were generated by the transformation and expression of T antigen and other oncogenes, however the expression of these genes did not result in a totipotent cell. For example, Robinson *et al.* (PNAS, 1994) teach that tsA58 can affect differentiation in certain cell types, however this was in terminal differentiation, not in the maintenance of a totipotent or pluripotent cell. In light of the art of record and as cited in the present specification, the specific genes taught in the present specification would not be considered genes that would prevent differentiation. Further, beyond broadly defining a differentiation-inhibiting gene by its resulting function when expressed, the specification fails to

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clearly describe any specific characteristic of a gene wherein one of skill in the art would be able to identify any particular polynucleotide sequence as a sequences which encodes or affects differentiation. As supported by the specific examples provided in the specification and specifically claimed the specification fails to provide the necessary guidance to make and use the instantly claimed composition which would meet the limitation set forth in the claim.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art and state of the art at the time of the claimed invention was made, it would have required undue experimentation to make and/or use the invention as claimed.

Applicants do not specifically address the above rejection in the after final amendment, therefore, the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 91-100, 103-105 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claim 91 is vague and confusing in the ability of the CICM cells from one cell line being capable of differentially expressing a transgene. It appears that all the cells contain the transgene in light of the recitation that the second CICM contains the transgene because of the limitation that it is not expressed. Further, it appears that

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both are totipotent, because the cells are from the same cell line and there is no indication that both populations of cells are not totipotent. Given that both populations are the same, it is unclear how one population of cells express a transgene and an identical population does not. Dependent claims do not further clarify the basis of the rejection because they only set forth how the CICM cells are specifically modified or cultured. These limitations further indicate that CICM cells are treated in the same manner, and none of these limitations provide a basis for obtaining two different gene expression patterns in one composition.

Applicants argue that the meaning of claim 91 is clear to persons skilled in the art. Applicants note the premise of the invention and argue that one of skill in the art would know that two different cells one expressing a transgene and one not expressing a transgene are comprised by the claim (see pages 5-6). Applicants' arguments have been fully considered but not found persuasive.

The claims are not directed to a product by process, and because the same CICM cell line is required for both the CICM cell line that expresses a transgene and on that does not express a transgene, the claims fail to clearly indicate how a single cell can comprise at least two different properties. Therefore, for the reasons above and of record, the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 91-95 and 101-105 stand rejected under 35 U.S.C. 102(e) as being anticipated by Sims *et al.* (US Patent 6,107,543).

Claims 91 and 92 encompass a composition of CICM cells wherein the cells contain a heterologous polynucleotide sequence. Dependent claims 93-95, 101 and 102 recite specific marker genes and specific properties of the cells. Dependent claims 103-105 are drawn to compositions which further comprise feeder cells. Patent '543 teaches ICM cells in culture. Sims *et al.* teach that the cells can be modified to contain any gene of interest, in particular selectable markers which result in selection against neomycin (columns 13-14). The inner cell mass cells (ICM) are capable of giving rise to blastocyst and live born calves (Table 1 and 4). Sims *et al.* teach similar methods for the isolation of inner ICM as those disclosed in the instant specification. Though Sims *et al.* do not specifically describe the specific morphology of the cells in culture or that the ICMs are alkaline protease positive and cytokeratin 18 negative, in light of the similarity of isolation techniques and similarity in other morphologies, the ordinary artisan would expect that the ICM cells of Sim *et al.* in '543 have the same characteristics as and that any specific properties would inherent. It is noted that where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a *prima facie* case of either anticipation or

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obviousness has been established. *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), *In re Ludtke*, 441 F.2d 660, 169 USPQ 563 (CCPA 1971), *Northam Warren Corp. v. D. F. Newfield Co.*, 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934) and MPEP 2112.01. Finally, *Sims et al.* teach various methods of culturing the cells, including culturing the cells on feeder cells. Thus, the compositions of ICM cells taught by *Sims et al.* anticipate the claims.

Applicants have argued that while *Sims et al.* suggest to transduce CICM cells with a gene of interest at the time of filing there was not a reasonable expectation that the cells would remain totipotent. See Applicants' amendment filed May 20, 2020, paper number 14, page 11. Applicants' arguments have been fully considered, but not found persuasive.

As indicated previously, upon review of instant disclosure and that of *Sims et al.* the methods for isolation and culturing CICM cells are very similar and one would expect that the resulting CICM cells would be identical to those describe in the present specification. Examiner would agree that *Sims et al.* did not reduce to practice a transgenic CICM cell or use said cell to generate a calf, however clearly *Sims et al.* had a reasonable expectation that this could be

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accomplished in providing the specific teachings for the introduction of a transgene. The guidance for the introduction of a transgene given in the present disclosure is not unique or novel. Further, it should be noted that the present specification does not reduce to practice a live calf which is capable or demonstrates that a transgene is contained in the germ cells of said animal, thus the instant disclosure does not reduce to practice experiments which clearly demonstrate that the cell after selection or various culturing conditions was totipotent. Applicants' arguments as they apply to present rejection are not convincing because in light of the specific teachings of each of the specifications there was an expectation that CICM cells transduced with a gene of interest would still be totipotent.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

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Claims 91-95, 98-105 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Sims *et al.* (PNAS 90:6143-6147, 1993), Deboer *et al.* (US Patent 6,013,857) and Stewart *et al.* (Dev. Biol. 161,626-628, 1994).

Claims 91-95 and 101-105 are summarized above. Claims 98-100 are directed to specific promoters for the expression of a transgene. Sims *et al.* teach methods of isolating ICM cells and specifically teach bovine ICM cells in culture. The ICM cells taught by Sims *et al.* were derived from a normal bovine, however they suggest that methodology could be extended and useful in the genetic modification of cattle (page 6146, bottom of second column). Deboer *et al.* teach at the time of filing methods for generating transgenic bovine were available. As noted above, it is not apparent that a CICM cell derived from a transgenic bovine would differ in its developmental properties from that derived from a bovine found in nature. The presence of a transgene does not alter the basic function of an CICM cell to promote development. However, if a distinguishable difference exists Deboer *et al.* teach a transgenic bovine from which ICM cells could be derived. The specific culturing methods of Sims *et al.* grow the bovine ICM cells in a disassociated suspension, not in the presence of fibroblast feeder cells. However, Sims *et al.* clearly indicate that further culturing systems which promote mitotic activity while inhibiting differentiation (page 6146, bottom of second column). In addition, Sims *et al.* teaches that most attempts to isolate and culture ICM cells are based on or adapted from the methods used to culture mice cells (page 6143, middle of second column-referencing early work of Evans and coworkers). Stewart *et al.* teach the isolation of mouse stem cells and primordial germ cells, and their ability to

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contribute to the germ line (summarized in the abstract). In particular, Stewart *et al.* successfully maintain the isolated cells by culturing the isolated cells on fibroblast feeder cells (page 626, bottom of second column). Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to use the methods taught in Stewart *et al.*, and used generally in the art to culture primordial cells and stem cells, for those taught in Sims *et al.* Sims *et al.* indicates the need for improved culturing methods and the indication that successful methods have been derived from those used in the mouse, and thus, one having ordinary skill in the art would have been motivated to substitute and optimize various successful methods used in the art for other ICM cells or ES cells derived from other species than mouse. There would have been a reasonable expectation of success given the successful results of Stewart *et al.* in culturing various sources of stem/primordial cells to extend and optimize if necessary culture conditions which maintain bovine ICM cells capable of contributing to the germ line.

In response to the previous rejection of record, Applicants summarize the teaching of each of the references and argue that none of the references demonstrate that CICM cells could be genetically manipulated without affecting the totipotency of the CICM cells. See Applicants' amendment, page 12. Applicants' arguments have been fully considered but not found persuasive. As noted above, Sims *et al.* in providing guidance for the production of transgenic CICM cells clearly providing that there was an expectation of success. Deboer *et al.* provide even more detailed guidance for particular genes and promoters for the production of transgenic

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animals and Stewart *et al.* provide evidence that at the time of filing conditions for culturing cells to maintain their totipotency were known and actively being optimized. In view of the art as a whole, Applicants' arguments that there was not a reasonable expectation that genetically manipulated cells would be totipotent are unconvincing since methods of maintain unmodified cells were known and used, and specific teachings for the genetic modification of said cells to produce transgenic animals was clearly taught.

Thus, absent evidence to the contrary, the claimed invention as a whole was clearly *prima facie* obvious.

Conclusion


No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach whose telephone number is (703)305-3732.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached at (703)305-4051.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group analyst Dianiece Jacobs whose telephone number is (703) 308-2141.

Joseph T. Woitach


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